DETAILED ACTION

Reasons for Allowance

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. R. Douglas Bradley (Reg. No. 44,553) on January 7, 2010.

2. The application has been amended as follows:

In the specification:

Replacing the abstract with--- The present invention provides methods for analyzing exon expression profiles of a cell or type of cell. In the invention, the expression levels of a plurality of individual exons or multiexons for each of a plurality of genes in the genome of an organism are measured and analyzed to determine the biological state, such as the exon expression state or transcriptional state, of the cell or type of cell. The methods of the invention are useful for determination of alternative RNA splicing in a plurality of genes. The invention also provides nucleic acid probe arrays for determining in parallel the expression levels of a plurality of exons or multiexons for each of a plurality of genes in the genome of an organism. [Such nucleic acid arrays comprise polynucleotide probes complementary and hybridizable to sequences in individual exons or multiexons. Methods for designing and making such nucleic acid probe arrays are also provided.] The invention further provides methods for

determining the effects of perturbations, such as perturbations by drugs, on exon expression and alternative RNA splicing pathways.

Replacing page 3, lines 29-31 with--- acids monitored without increasing probe density (see, *e.g.,* Friend et al., U.S. Patent Application Serial No. 09/364,751, filed on July 30, 1999, now abandoned; and Friend et al., U.S. Patent Application Serial No. 09/561,487, filed on April 28, 2000, now US Patent No.7,013,221 B1).

Replacing page 4, line 13 with--- Friend et al., U.S. Patent Application Serial No. 09/334,328 (filed on June 16, 1999, now US Patent No. 6,218,122 B1).

Delete www. in page 28, line 25, page 66, line 2, page 69, line 15,

Replacing page 31, lines 18-20 with--- 09/561,487 (filed on April 28, 2000, now US Patent No.7,013,221 B1); Friend et al., U.S. Patent Application Serial No. 09/364,751 (filed on July 30, 1999, now abandoned); Burchard, U.S. Patent Application Serial No. 09/616,849 (filed on July 14[6], 2000, now US Patent No. 7,371,516 B1).

Replacing "Application Serial No. 09/411,074, filed October 4, 1999 by Linsley and Schelter" in page 46, line 19 with--- Application Serial No. 09/411,074, filed on October 4, 1999 by Linsley and Schelter, now US Patent No. 6,271,002 B1.

In the claims:

Cancel claim 264.

Combining claims 46, 88, 212, 213, 266, and 267 with claims 1, 7-9, 14-28, 31-34, 36, 45, 86, 87, 89, 90, 263, 265, and 280-296.

1. (Currently Amended) A method for analyzing expression levels of different exon variants of a plurality of different genes in the genome of an organism in a cell sample derived from said organism, said method comprising measuring, *in vitro,* the [nucleic

acid] expression levels of [a plurality of] said different exon variants [of an exon of a gene, for each gene in said plurality of different genes in the genome of said organism from said cell sample], each of said different exon variants being a different splicing variant of each of said plurality of different genes [splice form of said exon] generated using a different 3' or 5' splicing site located in each of said plurality of different genes [splice junction of said exon]; and wherein said measuring step is performed by a method comprising:

(a) contacting a positionally-addressable array of polynucleotide probes with a nucleic acid sample comprising RNAs [or nucleic acids derived therefrom] from said cell sample or cDNAs transcripted from said RNAs under conditions conducive to hybridizations between said probes and said RNAs or said cDNAs [nucleic acids], wherein said array comprises a plurality of polynucleotide probes [of] comprising different nucleotide sequences [bound to different regions of a support], wherein said plurality of polynucleotide probes are bound to different regions of said array and comprises [a] variant junction probes that specifically hybridize[s] to [one of] said different exon variants and each of said variant junction probes is complementary and hybridizes to a junction region of two adjacent exons of one of said variants from said cDNAs[of an exon of a gene, for each gene in said plurality of different genes]; and

(b) measuring levels of hybridizations between said [plurality of polynucleotide] variant junction probes and said RNAs or said [nucleic acids] cDNAs[, wherein said levels of hybridization indicate the nucleic acid expression levels of said plurality of different variants; thereby] and analyzing the expression levels of said exon variants based on said levels of hybridizations.

17. (Currently Amended) The method of claim 1, wherein said plurality of polynucleotide probes is [in the range of] 1,000 to 50,000 different polynucleotide probes.

18. (Currently Amended) The method of claim 1, wherein said positionally-addressable array has [in the range of] 100 to 1,000 different polynucleotide probes per 1 cm^2.

19. (Currently Amended) The method of claim l, wherein said positionally-addressable array has [in the range of] 1,000 to 10,000 different polynucleotide probes per 1 cm^2.

20. (Currently Amended) The method of claim l, wherein said positionally-addressable array has [in the range of] 10,000 to 50,000 different polynucleotide probes per 1 cm^2.

36. (Currently Amended) The method of claim 1, wherein said [nucleic acid] expression levels are measured [as] by detecting abundance of mRNA transcripts.

89. (Currently Amended) The method of claim 86, further comprising performing the method of claim 1 using another nucleic acid sample derived from a cell sample of the same type not subjected to said perturbation and comparing the [nucleic acid] expression levels of at least a portion of said plurality of different exon variants in said nucleic acid sample derived from said cell sample subjected to said perturbation with the nucleic acid expression levels of said at least portion of said plurality of different exon variants in [a second] said another nucleic acid sample [derived from a cell sample of the same type not subjected to said perturbation].

90. (Currently Amended) The method of claim 89, wherein said comparing comprises determining the differences between the [nucleic acid] expression levels of each exon variant in said at least potion of said plurality of different exon variants in said nucleic acid sample derived from said cell sample subjected to said perturbation and the [nucleic acid] expression levels of the corresponding exon variants in said [second] another nucleic acid sample derived from a cell sample of the same type not subjected to said perturbation.

263. (Currently Amended) The method of claim 1, wherein said array of polynucleotide probes comprises one or more sets of successive overlapping probes covering [tiled along] the longest length exon [variant] among said cDNAs after the hybridizations [plurality of different variants of said exon].

265. (Currently Amended) The method of claim 86, wherein said perturbation is exposure of said cell sample to a drug.

266. (Currently Amended) The method of claim 86, wherein said perturbation is subjecting a genetic mutation in one or more genes of said plurality of different genes.

267. (Currently Amended) The method of claim 86, wherein said perturbation comprises [mutation of] mutating one or more genes of said plurality of different genes and exposure of said cell sample to a drug.

280. (Currently Amended) The method of any one of claims 32[,] and 263[, and 264 wherein each of said different nucleotide sequences consists of 15 to 200 nucleotides.

284. (Currently Amended) A method for analyzing expression levels of [exon] different splicing variants of a plurality of different genes in the genome of an organism in a cell sample derived from said organism, said method comprising:

(a) contacting a positionally-addressable array [of] comprising polynucleotide probes with a sample comprising RNAs [or nucleic acids derived therefrom] from said cell sample or cDNA transcripted from said RNAs under conditions conducive to hybridizations between said probes and said RNAs or [nucleic acids] said cDNAs, wherein said [array] probes on the array comprise[s] (i) [one] two or more exon specific probes comprising different nucleotide sequences [for] from each of [a] said plurality of different genes in the genome of said organism, wherein each of said different nucleotide sequences is complementary and hybridizes to a sequence within a different individual exon of one of said plurality of different genes; and (ii) a plurality of variant junction probes for each of a plurality of different splicing variants of [at least one exon for each gene in] said plurality of different genes, each of said different splicing variants [being a different splice form of said exon] is generated using a different 3' or 5' splicing site located in each of said plurality of different genes [splice junction of said exon], and each of said variant junction probes [being a probe specific] is complementary and hybridizes to a junction region of two adjacent exons of one of said variants from said cDNAs [and an adjacent exon in a multiexon comprising said variant of said exon], each of said exon specific probes and variant junction probes [being] are bound to a different region of said array and said array comprises a support; and

(b) measuring levels of hybridizations (i) between each of said exon specific probes and said RNAs or said [nucleic acids] cDNAs, and (ii) between each of said variant junction probes and said RNAs or said [nucleic acids] cDNAs[, wherein said levels of hybridization indicate the nucleic acid expression levels of said plurality of

different variants, thereby] and analyzing the expression levels of said [exon] variants based on said levels of hybridizations.

285. (Currently Amended) A method for analyzing expression levels of different splicing [exon] variants of a plurality of different genes in the genome of an organism in a cell sample derived from said organism, said method comprising:

(a) contacting a positionally-addressable array [of] comprising polynucleotide probes with a sample comprising RNAs [or nucleic acids derived therefrom] from said cell sample or cDNAs transcripted from said RNAs under conditions conducive to hybridizations between said probes and said RNAs or [nucleic acids] said cDNAs, wherein said [array] probes on the array comprise[s] a plurality of junction specific probes comprising different nucleotide sequences [for] from each of [a] said plurality of different genes in the genome of said organism [bound to different regions of a support], wherein said junction specific probes are bound to different regions of said array and each of said different nucleotide sequences is complementary and hybridizes to a sequence spanning a junction region of two adjacent exons in one of said cDNAs [a multiexon in a gene of the genome of said organism], and wherein said plurality of junction specific probes comprise[s] a plurality of variant junction probes for each of a plurality of different splicing variants of [at least one exon for] each gene in said plurality of different genes, each of said plurality of different splicing variants [being a different splice form of said exon] is generated using a different 3' or 5' splicing site located in each of said plurality of different genes [splice junction of said exon], [and] each of said variant junction probes [being a probe specific] is complementary and hybridizes to a junction region of two adjacent exons of one of said variants from said cDNAs and said

array comprises a support [and an adjacent exon in a multiexon comprising said variant of said exon]; and

(b) measuring levels of hybridizations between said plurality of variant junction probes and said RNAs or said [nucleic acids] cDNAs[, wherein said levels of hybridization indicate the nucleic acid expression levels of said plurality of different variants, thereby] and analyzing the expression levels of said [exon] variants based on said levels of hybridizations.

293. (Currently Amended) The method of claim 1, wherein said [method] measurement comprises measuring, *in vitro,* the [nucleic acid] expression levels of at least 5 of said different exon variants [of said exon].

294. (Currently Amended) The method of claim 293, wherein said [method] measurement comprises measuring, *in vitro,* the [nucleic acid] expression levels of at least 10 of said different exon variants [of said exon].

295. (Currently Amended) The method of claim 294, wherein said [method] measurement comprise measuring, *in vitro,* the [nucleic acid] expression levels of at least 100 of said different exon variants [of an said exon].

296. (Currently Amended) The method of claim 295, wherein said [method] measurement comprises measuring, *in vitro,* the [nucleic acid] expression levels of at least 1000 of said different exon variants [of said exon].

3. The following is an examiner's statement of reasons for allowance:

Claims 1, 7-9, 14-28, 31-34, 36, 45, 46, 86-90, 212, 213, 263, 265-267, and 280-296 are allowable in light of applicant's amendments filed on September 24, 2009 and the examiner's amendments. The rejections under 35 U.S.C. 112, first and second paragraphs

have been withdrawn in view of applicant's amendments filed on September 24, 2009 and the examiner's amendments. The closest prior arts in the record are Penn *et al.,* (WO 01/57252A2, priority date: February 4, 2000), Balaban *et al.,* (WO 01/081632 A1, priority date: April 25, 2000), DeRisi *et al.,* (Nature Genetics, 14, 457-460, 1996), and Friend *et al.,* (US Patent No. 6,165,709, filed on February 26, 1998). These prior arts do not teach or suggest the combination of steps a) and b) of claims 1, 284, and 285. These prior arts either alone or in combination with the other art in the record do not teach or reasonably suggest a method for analyzing expression levels of different exon variants of a plurality of different genes in the genome of an organism in a cell sample derived from said organism and a method for analyzing expression levels of different splicing variants of a plurality of different genes in the genome of an organism in a cell sample derived from said organism which comprise all limitations recited in claims 1, 284, and 285.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance".

4. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Frank W Lu /
Primary Examiner, Art Unit 1634
January 14, 2010